REMARKS

Claims 1, 2, 7 and 10 are now pending.

I. Written description

In order to promote prosecution of the subject application, the amendments made herein render this rejection moot.

II. Enablement

The Action rejects the claims as allegedly failing to comply with the enablement requirement. This rejection is respectfully traversed.

In order to promote prosecution of the subject application, the amendments made herein limit the claims to compounds A and J.

In view of the foregoing, Applicant respectfully requests that this rejection be withdrawn.

III. Obviousness

The Action alleges that the claims are unpatentable over WO 98/29375 ("Atlas") in view of US 6,303,139 ("Passi"). Applicant respectfully traverses the rejection.

In rejecting the claims as allegedly not enabled, the Action takes the position that only compound J is enabled, but not any of the other compounds or prodrugs within the scope of the claims.

More specifically, the Action notes that example 11 of the specification discloses the EAE test using compound J, and that this test is a standard animal model for MS. Therefore, as stated by the Action: "In light of that [example 11] it appears that applicant is enabled for treatment of MS with compound J."

However, in making the obviousness rejection, the Action takes the position that the mere suggestion of reducing oxidative stress, without any further showing or data, such as the animal

model of example 11 of the subject specification, is enough to render the subject claims obvious for treating MS, as required by the claims.

If the Action takes the position that "In light of that [example 11]" it appears that applicant is enabled for treatment of MS with compound J," is it not reasonable to assume that without such data (which neither Atlas not Passi provide) the skilled artisan would not regard it obvious to actually treat MS using compound J? There are myriads of compounds taught by the art (by Atlas and others) to generally have the ability to reduce oxidative stress.

For example, vitamin C and vitamin E are well known antioxidants and were thought to be promising candidates for treating MS. As shown by the attached abstract (Zhang, et al., Neurology, 57:75-80 (2001)), this was not the case.

Moreover, the attached table shows all current approved drugs for MS and all compounds that are in phase II or II for MS. As can be seen, none of the approved drugs are thought to treat MS due to antioxidant activities. And of the tested drugs, only one in phase II (inosine) is an antioxidant. And even this compound has a dual action - as an antioxidant and a promoter for rewiring of neurons.

Thus, in view of the state of the art and without any further and specific disclosure and experimental results specifically applicable to MS, would the skilled artisan regard each and every one of these antioxidant compounds, including compound J, as obvious to actually treat MS? How is this not, at best, an invitation to try?

To promote prosecution of the subject application, Applicant has significantly narrowed the scope of the claims to compound J and a specific prodrug, compound A. In the spirit of this compromise, Applicant respectfully requests that the examiner do the same and withdraw the above rejection.

CONCLUSION

In view of the above amendments and remarks it is respectfully submitted that the claims are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

Martin D. Moynihan
Registration No. 40,338

Date: June 22, 2009

Enclosure:

- Petition for Extension (Two Months)
- Request for Continued Examination (RCE)
- Zhang et al. Reference
- Current therapies for MS Reference

Current therapies for MS

ABC Treatments				
Condition/Symptom	**Generic Name**	**Comments**	**Brand Name**	**Manufacturer**
Relapsing-Remitting MS, Secondary Progressive MS with relapses	Interferon Beta 1a	30 mcg intramuscular once per week self-injection	Avonex	Biogen
		44 mcg subcutaneous 3 times per week self-injection	Rebif	Ares-Serono
	Interferon Beta 1b	Subcutaneous self-injection once every two days	Betaseron	Berlex
			Betaferon	Schering
Relapsing-Remitting MS	Glatiramer Acetate	20mg subcutaneous daily self-injection	Copaxone	Teva-Marion

Chemotherapeutic Agents				
Condition/Symptom	**Generic Name**	**Comments**	**Brand Name**	**Manufacturer**
Secondary Progressive MS, Worsening Relapsing-Remitting MS	Mitoxantrone	Intravenous every 3 months for about 2 to 3 years	Novantrone	Immunex
Potential, unlicensed treatments for Secondary Progressive MS and Worsening Relapsing-Remitting MS	Azathioprine	Anti-cancer treatments - currently unlicensed for use with MS	Imuran	Glaxo-Smith-Kline
	Cyclophosphamide	Anti-cancer treatments - currently unlicensed for use with MS	Cytoxan, Neosar	Bristol-Myers Squibb
	Cyclosporine	Anti-cancer treatments - currently unlicensed for use with MS	Sandimmune	Novartis Pharma

	Methotrexate	Anti-cancer treatments - currently unlicensed for use with MS	generic	Mylan
	Cladribine	Anti-cancer treatments - currently unlicensed for use with MS	Leustatin	

Corticosteroids & ACTH

Condition/Symptom	Generic Name	Comments	Brand Name	Manufacturer
Acute relapses in Relapsing-Remitting MS and occasionally Secondary Progressive MS	MethylPrednisolone	Intravenous high doses tapered off	Depo-Medrol	
			Solu-Medrol	Pharmacia
	Prednisone	Oral administration	Deltasone	Pharmacia
	Prednisolone	Intravenous administration	Delta-Cortef	Pharmacia
	Dexamethasone	Oral administration	Medrol	Pharmacia
			Decadron	Merck
	Adreno-corticotrophic Hormone (ACTH), Corticotropin	Use largely replaced by synthetic corticosteroids	Acthar	Roche, Rhone-Poulenc Rorer

Pain/Altered Sensation (Dysaesthesia)

Condition/Symptom	Generic Name	Comments	Brand Name	Manufacturer
Neuropathic/neurogenic pain (pain that arises from nerve dysfunction and not as a result of injury e.g. Trigeminal Neuralgia)	Carbamazepine	Anti-convulsant	Tegretol, Epitol, Atretol, Carbatrol	Ciba
	Gabapentin	Anti-convulsant	Neurontin	Pfizer
	Topiramate	Anti-convulsant	Topamax	Ortho-McNeil
	Zonisamide	Anti-convulsant	Zonegran	Elan
	Phenytoin		Dilantin	
	Desipramine		Norpramin	
	Amitriptyline	Tricyclic antidepressant	Elavil	AstraZeneca
	Imipramine	Tricyclic	Tofranil,	Ciba Geigy

		antidepressant	Imavate, Janimine	
	Doxepin	Tricyclic antidepressant	Sinequan, Adapin, Triadapin, Zonalon	
	Protriptyline	Tricyclic antidepressant	Vivactil	
	Cannabis and synthetic cannabinoids	Illegal in many parts of the world	Marinol	
Pain associated with poor circulation	Pentoxifylline		Trental	
'flu-like symptoms associated with Beta Interferon injections	Ibprofen		Neurofen	
			US versions	
	Aspirin		generic	
	Acetaminophen	Often formulated with alkaloid pain killers like codeine and hydrocodone	generic	
Paroxysmal itching	Hydroxyzine		Atarax	

Compounds for MS in Phase II and III

Phase III

- Alemtuzumab (brand name: Campath; under development by Genzyme and Bayer Schering) is a monoclonal antibody currently already used in the treatment of chronic lymphocytic leukemia and T-cell lymphoma.
- BG00012 (an oral fumarate ester under development by Biogen; anticipated brand name Panaclar).
- Cladribine (under development by Merck Serono; anticipated brand name: Movectro) is a antineoplastic compound with immunosuppressive effects. It is already currently used as an intravenous infusion to treat hairy cell leukemia (leukemic reticuloendotheliosis).
- Dirucotide (MBP8298), a synthetic myelin basic protein (MBP) consisting of 17 aminoacids, is currently in FDA fast-track for approval for SPMS.

- Fingolimod (under development by Novartis) is a sphingosine-1-phosphate receptor modulator for oral use.

- Laquinimod (under development by Teva and Active Biotech) is an immunomodulatory substance developed as an orally available disease modifying treatment in multiple sclerosis.

- Rituximab, trade names Rituxan and MabThera, is an anti-CD20 monoclonal antibody previously used against cancer, has shown damaging lesions reduction by 91% and relapses by 58%.

- Teriflunomide, the active metabolite of the antirheumatic drug leflunomide, is currently under investigation for treatment of MS.

Phase II

- ATL1102 (under development by Teva and Antisense Therapeutics) is a second-generation antisense inhibitor of CD49d, a subunit of VLA-4
- CDP323 (under development by UCB S.A. and Biogen) is a compound for oral intake acting against α4-integrin, i.e., it has the same mechanism of action as natalizumab.
- Daclizumab (brand name Zenapax; under development by Biogen and PDL) is an anti-IL2 monoclonal antibody and an immunosuppressant used to prevent rejection after organ transplantation..
- Estradiol and estrogen receptors(ER):
- Inosine: Inosine is a compound that has shown interesting preliminary results in phases I and II clinical trials. Two different mechanisms of action have been proposed. First, it produces uric acid after ingestion, which is a natural antioxidant; second, it has been shown to induce axonal rewiring in laboratory animals with stroke, and spinal cord injury[. However it can cause health problems in a long-term treatment mainly kidney stones.
- Tovaxin. Also a vaccine against T-Cells, which in this case consist of attenuated autoreactive T cells. It is developed by Opexa Therapeutics, (previously known as PharmaFrontiers
- Ocrelizumab, Anti-CD20 humanized monoclonal antibody, whose mechanism of action targets B-Cells, like Rituximab.
- Ofatumumab, other anti-CD20 monoclonal antibody, .
- Stem cell transplantation was found feasible in a phase I/II study in 21 patients with relapsing-remitting MS not responsive to interferon beta. It involves collecting some of the patient's own peripheral blood stem cells, giving low-intensity chemotherapy to eliminate auto-reactive lymphocytes, and then reinfusing the stem cells.
- BAF312, NOVARTIS' BAF312 is a sphingosine-1-phosphate receptor modulator for oral use that is currently (June 08, 2009) in Phase II trial.

Articles

Intakes of carotenoids, vitamin C, and vitamin E and MS risk among two large cohorts of women

S. M. Zhang, MD, ScD;, M. A. Hernán, MD, DrPH;, M. J. Olek, DO;, D. Spiegelman, ScD;, W. C. Willett, MD, DrPH; and A. Ascherio, MD, DrPH

From the Departments of Nutrition (Drs. Zhang, Willett, and Ascherio) and Epidemiology (Drs. Hernán, Spiegelman, Willett, and Ascherio), Harvard School of Public Health; and Channing Laboratory, Department of Medicine (Drs. Zhang and Willett), and Multiple Sclerosis Unit, Center for Neurological Diseases (Dr. Olek), Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

Address correspondence and reprint requests to Dr. S.M. Zhang, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115; e-mail; Shumin.Zhang@channing.harvard.edu

BACKGROUND: Antioxidant nutrients may reduce the risk of MS. In a recent case-control study, vitamin C intake was significantly inversely associated with MS risk among women. However, no prospective data are available.

OBJECTIVE: To examine prospectively the associations of intakes of carotenoids, vitamin C, and vitamin E with the risk of MS among women.

METHODS: The authors documented the occurrence of definite and probable MS within two large cohorts of women who completed detailed and validated semiquantitative food frequency questionnaires. One cohort (Nurses' Health Study) comprised 81,683 women aged 38 to 63 years in 1984, who were followed for 12 years; the other (Nurses' Health Study II) comprised 95,056 women aged 27 to 44 years in 1991, who were followed for 6 years.

RESULTS: The authors documented a total of 214 cases of MS. After adjustments for age, latitude of birthplace, pack-years of smoking, and total energy intake, the pooled multivariate relative risks (95% CIs) comparing women in the highest quintile with those in the lowest quintile were 1.1 (0.7 to 1.7) for α-carotene, 1.1 (0.7 to 1.6) for ß-carotene, 1.4 (0.8 to 2.2) for ß-cryptoxanthin, 1.0 (0.6 to 1.5) for lycopene, 1.0 (0.7 to 1.6) for lutein/zeaxanthin, 1.4 (0.9 to 2.1) for total vitamin C, 1.3 (0.9 to 2.0) for dietary vitamin C, 0.8 (0.6 to 1.3) for total vitamin E, and 0.9 (0.6 to 1.4) for dietary vitamin E. The authors found no associations between intakes of fruits and vegetables and risk of MS. Use of vitamin C, vitamin E, and multivitamin supplements was also unrelated to risk of MS.

CONCLUSIONS: These findings do not support hypotheses relating higher intakes of dietary carotenoids, vitamin C, and vitamin E to reduced risk of MS in women.